

Review

# Ocular toxicity of systemic anticancer chemotherapy

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## ABSTRACT\*

The increased use of chemotherapeutic agents has resulted in longer cancer patient survival. Consequently the ophthalmologist is seeing more patients with adverse ocular side effects secondary to these antineoplastic agents. Ocular toxicity induced by cancer chemotherapy includes a broad spectrum of disorders, reflecting the unique anatomical, physiological and biochemical features of the eye. Understanding the ocular side effects will assist the ophthalmologist and oncologist to recognize them early and intervene before blindness occurs. Anticipation of various treatment-related toxicities may also provide the opportunity for pharmacists to develop intervention strategies that could minimize or eliminate an expected side effect. The ophthalmologist should examine patients on anticancer therapy at baseline and three monthly thereafter. The various ocular side effects of anticancer chemotherapeutic agents, tamoxifen, and interferon on the adnexia, anterior segment, posterior segment and neuro-ophthalmic structures were reviewed.

**Keywords:** Anticancer drugs. Chemotherapy. Adverse drug effects. Tamoxifen. Interferon. Nigeria.

## RESUMEN

El uso progresivo de agentes quimioterápicos ha conseguido prolongar la supervivencia de los pacientes cancerosos. En consecuencia el oftalmólogo ve más pacientes con efectos adversos oculares de estos antineoplásicos. La toxicidad ocular inducida por quimioterápicos incluye un amplio espectro de desordenes que se reflejan en las condiciones únicas anatómicas, fisiológicas y estructurales del ojo. Entender los efectos adversos oculares ayudará al oftalmólogo y al oncólogo a reconocerlos en sus estados más tempranos e intervenir antes de que aparezca la ceguera. La anticipación a las diversas toxicidades oculares de los medicamentos puede proporcionar una oportunidad a los farmacéuticos para desarrollar estrategias que puedan minimizar o eliminar estos efectos esperados. El oftalmólogo debería examinar a los pacientes con anticancerosos en el inicio y después cada tres meses. Se revisaron los diversos efectos secundarios de los quimioterápicos, tamoxifeno e interferon sobre los órganos anejos, segmento anterior segmento posterior y estructuras neuro-oftálmicas.

**Palabras clave:** Antineoplásicos. Quimioterapia. Efectos adversos. Tamoxifeno. Interferon. Nigeria.

## (English)

## INTRODUCTION

Systemic drug-induced ocular side effects are increasing because of the vast numbers of new drugs being introduced.<sup>1</sup> Reports of drug-induced ocular toxicity must be well documented, and the other causes of these side effects ruled out to help establish causality. Systemic anticancer therapies can produce acute and chronic organ damage, but the eye is usually considered a protected site.<sup>2</sup> Consequently, it has been reported that the ocular side effects of cancer chemotherapeutic drugs are relatively uncommon.<sup>3</sup> Nonetheless, the oculo-visual system has a potentially high degree of sensitivity to toxic substances.<sup>2</sup>

A quarter of a century ago, the aim of cancer care was simply to cure the patient with little concern about the side effects of the treatment.<sup>4</sup> The increased use of chemotherapeutic agents has resulted in longer patient survival; consequently the ophthalmologist is seeing more patients with adverse ocular side effects secondary to these antineoplastic agents.<sup>5</sup> Ocular toxicity induced by cancer chemotherapy includes a broad spectrum of

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disorders, reflecting the unique anatomical, physiological and biochemical features of the eye.

Understanding the ocular side effects will assist the ophthalmologist and oncologist to recognize them early and intervene before blindness occurs. It is also essential to pharmacists involved in the clinical management of oncology patients.<sup>6</sup> Anticipation of various treatment-related toxicities may provide the opportunity for pharmacists to develop intervention strategies that could minimize or eliminate an expected side effect.

The ocular side effects will be grouped into adnexial, anterior segment, posterior segment and neuro-ophthalmic features. Apart from the standard chemotherapeutic agents, ocular side effects of other commonly used drugs such as interferon, which is used in haematological malignancies; tamoxifen and toremifene, which are used for the management of breast cancer, will be reviewed.

### OCULAR ADNEXIA SIDE EFFECTS

Structures of the skin including that of the face, eyelids and eyebrows may be affected by side effects of antineoplastic chemotherapy.<sup>7,8</sup> Among the cutaneous side effects are hyperpigmentation, which is common and acral erythema which is relatively specific to chemotherapy and is often dose related.<sup>7</sup> Miscellaneous, less frequent side effects are sclerodermiform dermatitis, Raynaud's phenomenon, photosensitivity and hypersensitivity syndrome.<sup>7-9</sup> Hypersensitivity reactions are most likely with L-asparaginase, taxans and platinum salts.<sup>9</sup> Some cutaneous side effects are relatively specific to one type of drug. Capillary leak syndrome is most often related to taxanes.<sup>7</sup> Hydroxyurea is responsible for some peculiar cutaneous side effects such as ulceration and pseudodermatomyositis, perhaps due to long term administration of the drug.<sup>7</sup> An exposure based cohort study of 52 patients designed to determine the prevalence of adnexial side effects of systemic 5-fluorouracil showed that the prevalence of blepharitis was 3.8%, eyelid dermatitis was 5.8%, cicatricial ectropion was 1.9%, tearing was 26.9% and punctal-canalicular stenosis was 5.8%.<sup>10</sup> Other cutaneous side effects include alopecia, phlebitis, chemical cellulitis, diffuse sclerosis, sterile folliculitis and flushing reactions.<sup>7,8,11</sup> Eccrine sweat or sebaceous gland involvement is more rarely reported.<sup>7</sup> Epiphora resulting from permanent lacrimal gland stenosis has been reported in patients receiving combination chemotherapy of cyclophosphamide, methotrexate and 5-fluorouracil.<sup>12,13</sup> Excessive tearing that resolves on cessation of treatment is commonly described as a side effect of 5-fluorouracil.<sup>13</sup> Alopecia, trichomegally and hypertrichosis have been reported as side effects of interferon therapy.<sup>14,15</sup>

In rare cases, the severity of these side effects may require interruption of therapy.

### ANTERIOR SEGMENT SIDE EFFECTS

Mucous membranes may be altered by several mechanisms including direct cytotoxicity, infection and a decrease in polymorphonuclear or platelet counts.<sup>7</sup> Megadoses of systemic chemotherapy such as carmustine and mitomycin can cause qualitative and quantitative changes in the tear film leading to damage to the corneal and conjunctival epithelium.<sup>16</sup> The calculated prevalence rates of ocular surface lesions with use of systemic 5-fluorouracil is ocular irritation, 5.8%; conjunctivitis, 3.8%; keratitis, 3.8%; tearing, 26.9%; and blurred vision, 11.5%.<sup>10</sup> Blacks were reported to have a significantly higher rate of tearing when compared with whites.<sup>10</sup> Corneal opacities have been reported with use of tamoxifen.<sup>5,17</sup> The keratopathy occurs in the form of subepithelial deposits, whorls and linear opacities.<sup>17</sup> Posterior subcapsular cataract can occur with busulphan,<sup>5,18-20</sup> methotrexate,<sup>5</sup> toremifene and tamoxifen.<sup>21-23</sup>

In a prospective study of breast cancer patients treated with tamoxifen and toremifene, annual cataract rates were found to be 6.8% and 6.2% respectively.<sup>22</sup> Combination chemotherapy comprising cyclophosphamide, methotrexate and 5-fluorouracil can cause ocular pruritus and or burning sensation.<sup>24</sup> 5-fluorouracil has been detected in tears within several minutes after intravenous 5-fluorouracil (peak concentrations as high as 60 micrograms/ml).<sup>24</sup> Combination chemotherapy for acute lymphoblastic leukaemia with standard doses of vincristine, cyclophosphamide or teniposide, cytarabine and asparaginase have been associated with corneal toxicity especially when cytarabine is used.<sup>25</sup> Symptoms consist of ocular pain, foreign body sensation, blurred vision and bilateral conjunctival hyperaemia.

Interferon when used in the management of haematological malignancies or hepatitis is associated with side effects in the anterior segment of the eye.<sup>26,27</sup> Acute corneal allograft rejection has been reported with the use of alpha-2 interferon.<sup>26</sup> The development of glaucoma during the course of treatment with interferon alpha has also been reported.<sup>27</sup> The mechanism by which interferon therapy might lead to glaucoma remain unclear, but the glaucoma disappeared after the drug therapy was discontinued.

### POSTERIOR SEGMENT SIDE EFFECTS

Posterior segment lesions are important because of the marked visual loss that can occur. Visual loss secondary to retinopathy occurs with the use of cisplatin.<sup>28-31</sup> Visual loss may be bilateral and irreversible and visual fields shows bilateral central scotomas.<sup>29</sup> Visual evoked response and electroretinogram have been used to document the retinotoxicity of cisplatin and etoposide.<sup>30</sup> Electroretinogram showed a markedly reduced a-wave amplitude and absent b-waves.<sup>29</sup> Autopsy showed splitting of the plexiform layer consistent with the loss of the electroretinogram b-wave. Retinal ischaemia and neovascularization have been reported with use of cisplatin in a patient on

combination chemotherapy (bleomycin, etoposide and cisplatin).<sup>32</sup> A case of apparent acceleration of retinitis pigmentosa with blindness following cytotoxic chemotherapy for non-Hodgkin's lymphoma has been reported.<sup>33</sup> The involved patient probably had Usher's syndrome (congenital sensorineural deafness).

Retinopathy also occurs with mitotane and tamoxifen.<sup>5</sup> Tamoxifen can cause bilateral pigmentary retinopathy severe enough to warrant discontinuation of therapy.<sup>17</sup> Tamoxifen and toremifene may also cause macular crystals, macular drusen and yellowish spots in the macula area.<sup>22</sup> The prevalence of refractile retinal opacities in patients on tamoxifen has been shown to be 3.1% (mean duration of therapy-806 days).<sup>34</sup>

Interferon is also a known cause of retinopathy.<sup>35-37</sup> Interferon associated retinopathy is typically characterized by retinal haemorrhages and cotton wool spots in the posterior fundus but visual function is usually maintained.<sup>35,36</sup> Macula oedema with reduced visual acuity may however occur.<sup>35</sup> Interferon-induced ischaemic retinopathy can occur in asymptomatic cancer patients.<sup>37</sup> These retinal changes are usually reversible with discontinuation of therapy. This underscores the importance of dilated funduscopy at baseline and during follow-up, at least every 3 months, for all cancer patients receiving interferon to identify retinal toxicity at its earliest stages.

#### NEURO-OPHTHALMIC SIDE EFFECTS

Antineoplastic chemotherapy can cause damage to the optic nerve and the ocular motor nerves especially carmustine, vinblastine and vincristine.<sup>5</sup> Generally, neurotoxic side effects of chemotherapy occur frequently and are often a reason to limit the dose of chemotherapy.<sup>38</sup> Chemotherapy may cause both peripheral neurotoxicity consisting mainly of a peripheral neuropathy and central neurotoxicity, ranging from minor cognitive deficits to hemiparesis, aphasia, aseptic meningitis, encephalopathy with dementia or even coma.<sup>38</sup> The vinca alkaloids, cisplatin and the taxanes are among the most important drugs inducing peripheral neuropathy. Methotrexate, cytarabine and ifosfamide are primarily known for their central neurotoxic effects.<sup>38</sup>

There is hardly a cytostatic agent, which does not exercise a side effect on the nervous system.<sup>39</sup>

The mechanism of visual toxicity induced by cisplatin is unknown but may result from central nervous system accumulation of drug after repeated doses, especially with high-dose platinum containing regimens.<sup>30</sup> Toxic neuropathies including disc oedema, retinal oedema and optic neuritis are rare, but have been described as occasional side effects of treatment with cisplatin.<sup>40</sup>

Tamoxifen has been reported to cause bilateral optic neuritis followed by optic atrophy and visual loss.<sup>17</sup> This effect is dose related. Interferon may also cause neuro-ophthalmic lesions. Ischaemic optic neuropathy which may be bilateral, presenting with optic disc oedema and progressing to optic atrophy has been reported with the use of interferon.<sup>41-43</sup> Interferon-alpha treatment may cause or aggravate the risk of developing anterior ischaemic optic neuropathy and vulnerable patients should be advised of this potential complication.<sup>43</sup>

#### SECOND ORBITO-OCULAR MALIGNANCY

Many agents used in cancer chemotherapy are known carcinogens. However, few secondary malignancies have been definitely linked to chemotherapy, since studies on this problem are complicated by methodological problems.<sup>44</sup> A causal relationship has been established between alkylating agents and leukaemia and between cyclophosphamide and bladder cancer.<sup>44</sup> In the orbito-ocular region, pleomorphic adenoma of the lacrimal gland has been reported in a child after treatment of acute lymphoblastic leukaemia.<sup>45</sup>

#### CONCLUSION

Anticancer chemotherapy, tamoxifen and interferon can cause considerable ocular morbidity. They can cause marked irreversible visual loss even at therapeutic doses. Thus the ophthalmologist should examine patients on anticancer therapy at baseline and three months thereafter. The oncologist and pharmacists need to be aware of the possibility of ocular complications in order to develop intervention strategies that could minimize or eliminate an expected side effect.

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